II. Miscellaneous

On page 2 of the Office Action, the Examiner indicates that many references cited in the Information Disclosure Statement submitted in parent U.S. Application No. 09/276,820 were not found in that application. Accordingly, the Examiner has requested that Applicants provide copies of references AC2, AN2 and AO2. Accordingly, Applicants provide copies of these documents. Furthermore, Applicants provide the English abstract for AO2 in the first Information Disclosure Statement submitted with this application , cited as AT24.

On page 3 of the Office Action, the Examiner objects to claims 83, 88, 92 and 100–102, as well as to claims dependent thereon, on the grounds that the objected claims depend from non-elected claims. Accordingly, these claims have been amended so that they depend only from currently pending claims.

III. The Rejections

A. The Rejection Under 35 U.S.C. § 112 Second Paragraph

On page 3 of the Office Action, claims 81, 83–88, 92 and 100–103 have been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that they are indefinite. Applicants respectfully traverse the rejection in view of the following discussion.

On page 4 of the Office Action, claims 81 and 100 (and dependent claims) have been rejected as indefinite in the recitation of "endogenous gene" or "endogenous cellular gene."

First, Applicants point out that neither claim contains the term "endogenous cellular gene."

During the prosecution of U.S. Application No. 09/481,375, the Examiner set forth the same rejection in the Office Action dated September 8, 2001. On page 8 of the Office Action in that case, the Examiner set forth a rejection of claims 69, 73, 81, 82, 88, 106, 110 and 111 (and dependent claims) on the grounds that they were indefinite for reciting the term "endogenous gene." The rationale was the same as in the present application: "it is not clear whether the gene is a gene in its native chromosomal locus or a gene that was, at one time, introduced externally, for example, a gene in a transgenic animal that is not native to the animal's genome."

In an interview regarding this point, Applicants explained that any sequence that is in the cell prior to introducing the vector would have been understood to constitute an "endogenous" sequence, according to the invention. In Applicants' Response in 09/481,375, on page 18, Applicants responded as follows:

> Applicants point out that all of the above-mentioned claims are limited to integrating the vector into the cellular genome. The claims are also directed to expressing an endogenous gene in the genome. Accordingly, as long as the gene is a part of the genome, it would have been understood to be an endogenous gene. This includes a gene in its native chromosomal locus, a gene that is native to the organism but in other than its native chromosomal locus, a gene originally introduced

> exogenously, for example, in a transgenic animal, transposed viral sequences in a cell, duplicated copies of a sequence in a cell, and the like. Applicants respectfully submit that the person of ordinary skill would have understood the term and the claims to refer to the activation of genes in a cellular genome. Accordingly, any gene in a cellular genome, regardless of when or how it originated, would have been understood as encompassed by the claims. Applicants submit, therefore, that the claims are definite.

Following Applicants' Response, the Examiner withdrew the rejection of all claims, except for claim 69. He indicated that the rejection was maintained as to claim 69 because the claim did not make it clear that the endogenous gene is over-expressed from the cellular genome and not from the integrated vector. Accordingly, in the present case, Applicants adopt the same argument that overcame the rejection as to claims 73, 81, 82, 88, 106, 110, and 111 and, in addition, point out that the present claims clearly recite that over-expression is from a sequence in the cellular genome and not from a vector sequence integrated into the genome. Accordingly, Applicants believe that the rejection on this ground has been overcome.

On page 4 of the Office Action, claim 81 (and dependent claims) is rejected as indefinite in the recitation of "over-expressing" and "over-expression." In U.S. Application No. 09/481,375, the Examiner set forth the same rejection for claims 69, 73–75, 78, 81, 82 and 85 (and dependent claims) with the same rationale. See page 8 of the Office Action dated September 8, 2001. In Applicants' Response, in the paragraph spanning pages 18–19, Applicants explained as follows:

> Specifically, the Examiner questions whether over-expression applies to expression levels relative to "endogenous genes (prior to activation) and/or relative to other cells expressing the same or different gene products." This term is discussed in the specification as the Examiner's first definition. See page 7 of Applicants' specification. In view of this and many other sections of the Applicants' specification, Applicants submit that the person of ordinary skill would have understood that the term "over-expression," in the context of the Applicants' invention, refers to an increase in expression in a given cell relative to the level of expression in the cell prior to integration of Applicants' vector. Page 7, for example, refers to cells over-expressing an endogenous gene that has been activated or has undergone increased expression. Applicants submit that this concept would have been understood since the specification is replete with reference to activation of gene expression of endogenous genes by integration of Applicants' vector. Further, the claims recite that over-expression is caused by up-regulation of the gene by the integrated vector in the cells.

The Examiner subsequently withdrew the rejection of all of these claims. In the present case, Applicants adopt the same argument. They also point out that the claims in the present case already recite that over-expression is caused by upregulation of the cellular gene by the integrated vector. Accordingly, Applicants believe they have overcome the rejection on this ground.

On page 4 of the Office Action, claim 81 (and dependent claims) is rejected as being indefinite in the recitation of "expression product" and "portion thereof." Applicants point

out, however, that neither of these terms is found in (canceled) claim 81. Furthermore, these terms are not found in any of the claims that were dependent upon claim 81. Accordingly, absent further argument, Applicants believe this rationale for rejection has been set forth in error. Appropriate comment is respectfully requested.

In the paragraph spanning pages 4 and 5 of the Office Action, claim 81 (and dependent claims) has been rejected as indefinite in the recitation of "screening said cell." The Examiner states that a screening step is not needed in the claim. This step is not recited in the present claims. Accordingly, Applicants believe that the rejection on this ground has been overcome.

On page 5 of the Office Action, claim 81 (and dependent claims) has been rejected for the recitation of "said isolated and cloned cell" because there is no antecedent basis for this limitation. This phrase is not recited in the present claims. Accordingly, Applicants submit that the rejection on this ground has been overcome.

On page 5 of the Office Action, claim 81 (and dependent claims) is rejected as being incomplete on the grounds that the method steps do not clearly relate back to a method for over-expressing an endogenous gene in a cell *in vivo* and on the further ground that the method steps do not have a step that actually recites over-expression of an endogenous gene *in vivo*. Applicants believe that this ground of rejection is not meant to apply to (canceled) claim 81. The

Examiner states that step (e) recites culturing cells, but step (e) in (canceled) claim 81 recited introducing a cell into an animal.

The above argument notwithstanding, Applicants submit that this ground of rejection is moot in view of the amended claims.

A further ground of rejection of claim 81 is that it is unclear whether the method steps involve the introduction of a vector into a cell *in vitro* or systemic introduction *in vivo*. Accordingly, the amended claim recites that the vector is first introduced into a cell *in vitro*. Accordingly, Applicants submit that this ground of rejection has been addressed and overcome.

On page 5 of the Office Action, claim 81 (and dependent claims) has been rejected as indefinite in the recitation of method steps (b) and (e) on the grounds that the limitations "do not represent active process steps subject to control of the artisan." Specifically, the Examiner questions what is meant by "integrating said construct into the genome by non-homologous recombination." Applicants believe that "integrating said construct into the genome by non-homologous recombination" would be clear to the person of ordinary skill in the art. Nevertheless, Applicants have submitted new claims using language that has been accepted by the Patent Office as explained below.

Applicants believe that step (b) in Applicants' new claims is definite. The claims recite that the step involves "maintaining" the cell under conditions for non-homologous

recombination of the vector with the cell, thereby producing a non-homologously recombinant cell. Exhibit A, attached, contains issued claims directed to this step, but involving homologous recombination rather than non-homologous recombination. In Exhibit A, claim 59, step (b) recites "maintaining [the cell] under conditions appropriate for homologous recombination thereby producing a homologously recombinant cell." Since the new claims copy this language, the recitation in the new claims should be definite.

Step (c) in Applicants' new claims recites that over-expression is accomplished by "maintaining" the non-homologously recombinant cell under conditions appropriate for over-expression of the endogenous gene. This recitation should be definite. Exhibit A, claim 59, step (c), recites "maintaining the homologously recombinant cell *in vitro* under conditions appropriate for expression of the gene, thereby making the protein." Since the new claims copy this language for over-expressing the recited gene, this recitation in the new claims should be definite.

Step (c) in Applicants' new claims also recite that the cell is introduced into the animal "thereby over-expressing" the endogenous gene in the cell introduced into the animal. This also should be definite. Exhibit B, claim 15, recites an active step of "introducing" the gene trap cassette "wherein said cassette is non- homologously incorporated into the genome...and said splice donor sequence...is spliced to a splice acceptor sequence..." Accordingly, Applicants believe that an active step of introduction wherein a result is achieved is considered definite by the Patent Office. Applicants' claims likewise recite an active step of introduction

whereby a specific result is achieved. Therefore, Applicants' amended claims, with respect to this recitation in step (c), also should be definite.

Accordingly, Applicants believe that this ground of rejection has been addressed and overcome.

On page 6 of the Office Action, claim 92 has been rejected on the grounds that the limitation "said vector construct" does not contain sufficient antecedent basis. The term "construct" is not recited in amended claim 92. Accordingly, Applicants believe that this ground of rejection has been addressed and overcome.

Applicants believe that all grounds of rejection under 35 U.S.C. § 112, second paragraph, have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection on all grounds is, therefore, respectfully requested.

B. The Rejections Under 35 U.S.C. § 112 First Paragraph

On page 6 of the Office Action, claims 81, 83–88, 92 and 100–103 have been rejected under 35 U.S.C. §112, first paragraph, as not enabled. Applicants respectfully traverse the rejection.

Based on the Office Action, the rationale for the rejection appears to be that the invention lacks utility because cell therapy is an inoperable embodiment and no other useful

embodiments are asserted. But if this is the case, the claims ought to be rejected under § 101 as well as § 112-1. Since a rejection under § 101 is not made, the Examiner must believe the claims have some other utility. It is unclear from the Office Action, however, what the Examiner regards as this utility.

This point was clarified by the Examiner in a telephone call made by Applicants' attorney on May 9, 2001. The Examiner explained that he believes that the claims encompass use for cell therapy and that cell therapy meets the requirements of § 101. Therefore, the claims were not rejected under § 101.

The Examiner explained that his rationale for rejecting the claims is that the only specific, substantial, credible, or well-established utility is cell therapy and this is not enabled by the specification. On page 10, the Examiner stated:

> ...the instant disclosure does not provide evidence of a specific, substantial, credible, or well-established utility for non-therapeutic *in vivo* administration of the recombinant cells of the claimed invention.

However, on page 7 of the Office Action, the Examiner states that there are two specific utilities as follows: "the only specific utility for the claimed method described in parent application, U.S. Application No. 08/941,223, is in the context of *cells* to be used *in vivo* to provide the gene product in the intact animal...or for use of "cells produced by this method...[to]

be used...*in vivo* (e.g., for use in cell therapy)..." (Emphasis added). Accordingly, the Examiner takes the position that producing an expression product *in vivo* has specific utility.

In the interview, the Examiner explained that he found specific utility for using the cells to express a gene product *in vivo* (for other than cell therapy) but not substantial utility. Accordingly, the Examiner rejected the claims as lacking enablement on the grounds that the only substantial or well-established utility for using the cells to produce a gene product *in vivo* was for cell therapy.

Applicants disagree for the reasons that follow and assert that (1) protein production *in vivo*, not limited by the specification to cell therapy, *per se*, has both substantial and well-established utility and (2) the specification also discloses isolation and purification of proteins made *in vivo*, which also have substantial and well-established utility.

Substantial Utility in Fact

The term "substantial utility" is defined as a utility that defines a real world use. Utility Guidelines Training Materials, page 6. In the present case, using cells *non-therapeutically* to produce a desired protein in an animal had real world uses at the time of Applicants' earliest filing.

These uses are discussed in the attached Declaration by Dr. John J. Harrington, an inventor in the above-captioned application. Dr. Harrington discusses various ways in which

cells introduced into an animal, and which produce protein in the animal, were used in the art. The opinions and conclusions in the Declaration are based on evidence in the form of scientific references available in the art at the time that Applicant's earliest priority application was filed. These references show that it was useful to introduce a cell into an animal to produce a desired protein from that cell where the cell is not used for cell therapy. Accordingly, based on discussion and evidence in the Declaration, methods for expressing protein from cells introduced into an animal had real-world use besides for cell therapy. Because these methods had utility, Applicants' methods would likewise have had the same utility.

Accordingly, the Examiner is respectfully directed to Dr. Harrington's discussion and evidence discussed in the Declaration. Based on the discussion and evidence in the Declaration, Applicants assert that the claimed methods had a non-therapeutic, real-world use. Thus, Applicants believe that they have met their burden for showing a substantial utility besides cell therapy.

Credible Utility for In Vivo Protein Production

"Credible utility" is based on "whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided." Applicants respectfully submit that the utility of the production of a desired protein in an animal would have been believable to the person of ordinary skill in the art at the time that the application was filed based on the evidence and discussion in the Declaration.

Well-Established Utility

"Well-established utility" is defined as "a specific, substantial and credible utility, which is well-known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art." Utility Guidelines Training Materials, page 7. Applicants submit that the using cells non-therapeutically to produce a desired protein in an animal had well-established utility at the time of Applicants' earliest filing.

The issue of well-established utility is discussed in the attached Declaration. Scientific evidence showing well-established utility is in the form of references from the scientific literature available to the person of ordinary skill in the art at the time that Applicants' earliest application was filed. The references show that non-therapeutic *in vivo* expression of proteins from implanted cells was a developed art at the time of filing. Accordingly, the person of ordinary skill in the art would have known of the non-therapeutic utility of protein expression from cells introduced into an animal. Applicants' specification teaches protein expression from cells introduced into an animal. Because the non-therapeutic utility of protein expression from cells introduced into an animal was known to the person of ordinary skill, the non-therapeutic utility of Applicants' methods would have been readily apparent.

Thus, the Examiner is respectfully directed to the attached Declaration for the discussion and evidence supporting these assertions. Based on the evidence in the Declaration,

Applicants believe that they have met their burden of showing that the non-therapeutic use of Applicants' claimed methods was a well-established utility.

Substantial Utility Disclosed

The Examiner has also asserted that the only real-world use *disclosed* in the specification was for cell therapy. Applicants respectfully disagree. The isolation and purification of proteins produced by cells introduced into an animal *in vivo* is disclosed in Applicants' specification. These have a real-world use. References discussed in the Declaration are evidence of this use.

However, Applicants point out that even if the isolation and purification of these proteins had not been disclosed, the claimed method still would have had a well-established utility. Please see the section headed "Well-Established Utility."

Assertions of Utility in U.S. Application No. 08/941,223

Applicants' specification discloses the utility of isolating the protein produced *in vivo*. For the Examiner's convenience, the relevant text is given below.

Page 7, lines 3–9

- The cell over-expressing the gene can be cultured *in vitro* so as to produce desirable amounts of the gene product of the endogenous gene whose expression has been activated or increased. The gene product can then be isolated and purified.

Alternatively, the cell can be allowed to express the desired gene product *in vivo*.

Page 8, lines 10–17

- The invention also encompasses methods for using the cells described above to overexpress a gene that has been characterized (for example, sequenced), uncharacterized (for example, a gene whose function is known but which has not been cloned or sequenced), or a gene whose existence was, prior to over-expression, unknown. The cells can be used to provide desired amounts of a gene product *in vitro* or *in vivo*. The gene product can then be isolated and purified if desired. It can be purified by cell lysis or from the growth medium (as when the vector contains a secretion signal sequence).

Page 9, lines 4–9

- The invention accordingly is also directed to methods of using libraries of cells to overexpress endogenous genes. The library is screened for the expression of the gene and cells are selected that express the desired gene product. The cell can then be used to purify the gene product for subsequent use. Expression in the cell can occur by culturing the cell *in vitro* or by allowing the cell to express the gene *in vivo*.

Page 13, lines 1–2

- The methods are also capable of producing over-expression of known and/or characterized genes for *in vitro* or *in vivo* protein production.

Page 16, lines 9–15

- The cell over-expressing the gene can be cultured *in vitro* so as to produce desired amounts of the gene product of the endogenous gene that has been activated or whose expression has been increased. The gene product can then be isolated and purified to use, for example, in protein therapy or drug discovery.

  Alternatively, the cell expressing the desired gene product can be allowed to express the gene product *in vivo*.

Pages 16–17, lines 25–30 and 1–2

- The cell over-expressing the gene is cultured such that amplification of the endogenous gene is obtained. The cell can then be cultured *in vitro* so as to produce desired amounts of the gene product of the amplified endogenous gene that has been activated or whose expression has been increased. The gene product can then be isolated and purified.

  Alternatively, following amplification, the cell can be allowed to express the endogenous gene and produce desired amounts of the gene product *in vivo*.

Page 17, lines 11–17

- The cell over-expressing the gene can be cultured *in vitro* so as to produce desirable amounts of the gene product of the endogenous gene whose expression has been activated or increased. The gene product can then be isolated and purified.

  Alternatively, the cell can be allowed to express the desired gene product *in vivo*.

Page 29, lines 24–25

- Cells produced by this method can be used to produce protein *in vitro* (e.g., for use as a protein therapeutic) or *in vivo* (e.g., for use in cell therapy).

Page 35, lines 21–26

- The invention is also directed to methods of using libraries of cells to over-express an endogenous gene. The library is screened for the expression of the gene and cells are selected that express the desired gene product. The cell can then be used to purify the gene product for subsequent use. Expression of the cell can occur by culturing the cell *in vitro* or by allowing the cell to express the gene *in vivo*.

As is clear from the above text, isolation and purification of the protein produced in the animal are disclosed. The utility was substantial and also would have been readily apparent to the person of ordinary skill in the art. See the references addressed in the Declaration that disclose isolating and purifying protein produced *in vivo*.

Accordingly, the specification asserts utilities other than cell therapy that are specific, substantial, credible, and well-established.

Enablement

As discussed herein above, the Examiner's basis for rejecting the claims under § 112 is that the only substantial, or well-established utility for using cells to produce a gene product *in vivo* is cell therapy. Since Applicants have now shown substantial and well-

established utility for using cells to produce a gene product *in vivo* besides cell therapy, Applicants believe they have overcome the basis of rejection.

Applicants finally point out that the case law has established that a claim may embrace some inoperative embodiments without violating either § 101 or § 112-1. *Atlas Powder Company v. E. I. DuPont de Nemours and Co.,* 750 F2d 1569; 224 USPQ 409 (Federal Circuit 1984). According to this case, it is not the function of claims to specifically exclude possible inoperative embodiments. Where, however, a patent claim specifically calls for a result that does not occur, the claim may fail to meet the utility requirement. *Raytheon Co. v. Roper Corporation,* 724 F2d 951; 220 USPQ 592 (Federal Circuit 1983). In the present case, the Applicants' claim does not specifically call for a result which does not occur because it is not directed to cell therapy. The claim is simply directed to a method for producing protein. Therefore, even if the claim is construed as encompassing an inoperative embodiment, under the cited case law, the claim meets the requirements of § 112-1.

In view of the above argument and evidence that Applicants have provided, Applicants respectfully submit that the grounds of rejection have all been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

C. The Rejection Under 35 U.S.C. § 102

On page 11 of the Office Action, claims 81, 83, 86, 87, 92 and 100–102 have been rejected under 35 U.S.C. § 102(e) on the grounds that they are anticipated by U.S. Patent No. 6,136,566 to Sands et al., herein "Sands" and as further evidenced by Vasallo et al. (Biochemical and Biophysical Research Communications, Vol. 270, pages 1036–1040 (2000)), herein "Vasallo." Applicants respectfully traverse the rejection.

Sands is relied upon for disclosing a method for producing an expression product of an endogenous cellular gene *in vivo* by introducing a vector comprising a transcriptional regulatory sequence in an embryonic stem cell, integrating the vector into the genome of the cell by non-homologous recombination, over-expressing an endogenous gene or portion thereof by upregulation of the gene by the transcriptional regulatory sequence, screening the cell for over-expression of the endogenous gene and introducing the isolated and cloned cell into an animal under conditions favoring the creation of transgenic animals over-expressing the endogenous gene by the cell *in vivo*.

Applicants provide new claim 106. This claim is limited to producing protein from the endogenous gene in the animal. Sands neither discloses nor suggests the production of protein from the endogenous gene either *in vitro,* in the cell introduced into an animal, or in the transgenic animal. Sands actually teaches away from translation of the endogenous gene, in either context, as is discussed below.

The Sands vectors at issue contain a selectable marker 3′ to a promoter and linked to a 3′ splice donor. The marker lacks a poly A site. The poly A site is supplied by the trapped gene. When a gene is trapped, therefore, a fusion transcript is produced containing marker RNA and RNA from the trapped gene. The marker RNA is translated, but the RNA from the endogenous gene is not translated. The purpose of producing RNA from the endogenous gene is to provide nucleic acid sequence information about the gene.

The goal of Sands is to provide a "knock-out" mouse for every gene in the genome and to use the mouse to determine the function of the gene. Towards this goal, the identity of each "knocked-out" gene is determined. Thus, the Sands' vectors provide two functions: "knock-out" and identification of a gene. Accordingly, the vectors contain sequences that disrupt expression of a gene and sequences that produce a fusion transcript between the marker and the endogenous gene. The disrupted gene is identified by endogenous gene sequences on the fusion transcript. Accordingly, identification is by nucleic acid sequencing only. For uses of the fusion transcript, see Sands, column 4, lines 10-31; column 4, lines 45-50; Figures 2-6; column 5, lines 8-30; column 6, lines 11-25; column 11, 5.2.2; column 13, 5.3; and column 14, lines 1-15.

Thus, Sands does not disclose or suggest the production of a protein from the endogenous gene either *in vitro* or *in vivo*. On the contrary, Sands specifically teaches away from producing protein from the endogenous gene.

> "All of the traps of the VICTR series are designed such that a fusion transcript is formed with the trapped gene. For all but VICTR 1, the fusion contains cellular exons that are located 3′ to the gene trap insertion. All of the flanking exons may be sequenced according to the methods described in the following section. To facilitate sequencing, specific sequences are engineered onto the ends of the selectable marker (e.g., puromycin coding region). Examples of such sequences include, but are not limited to unique sequences for priming PCR, and sequences complementary to the standard M13 forward sequencing primer. **Additionally, stop codons are added in all three reading frames to ensure that no anomalous fusion proteins are produced.** All of the unique 3′ sequences are followed immediately by the synthetic 9 base pair splice donor sequence. This keeps the size of the exon comprising the selectable marker (puro gene) at a minimum to best ensure proper splicing, and positions the amplification and sequencing primers immediately adjacent to the flanking "trapped" exons to be sequenced as part of the construction of a library database."

Emphasis added. See Sands, column 10, lines 4–23.

This shows that Sands obtains expression of the endogenous gene only to obtain nucleic acid sequence information. Protein expression is neither disclosed nor suggested. In fact, Sands teaches preventing protein expression from the endogenous gene to avoid problems with marker expression that could result from the production of anomalous fusion proteins produced by fusion of a marker protein with protein from the endogenous gene. Moreover, to express the endogenous protein would defeat the purpose, which was to knock-out endogenous

gene expression. Accordingly, Sands teaches away from the production of endogenous protein sequences both *in vitro* and *in vivo*.

Applicants also provide new claim 107. This claim recites that the expression product of the endogenous gene is detected after the cell is in an animal. Sands neither discloses nor suggests detecting the expression product (i.e., transcript) in an animal. Detection of this expression product is for sequencing purposes only. Sequencing is done in order to identify the disrupted gene. Therefore it is always performed *prior* to making the mouse. Thus, Sands does not suggest or discuss detecting the expression product of the endogenous gene after the cell has been introduced into an animal.

In summary, the Sands vectors are designed to knock out gene function. None of the vectors produce the protein product of the knocked-out gene. To do so would, in fact, defeat the purpose, which is to knock out the gene. The only use of the fusion transcript is to identify the knocked-out gene by its nucleic acid sequence.

In view of the above discussion and Applicants' amendment, Applicants submit that all grounds for the rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

D. The Rejection Under 35 U.S.C. § 102(e) or § 102(a) or § 103(a)

On page 12 of the Office Action, claims 81, 83–88, 92 and 100–103 have been rejected under 35 U.S.C. § 102(e) or § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Treco *et al.*, U.S. Patent 5,641,670, herein "Treco," as evidenced by Capecchi, (Scientific American 270:52-59 (1994)), herein "Capecchi." Applicants respectfully traverse the rejection.

Capecchi is cited as showing that most of the insertion events with the targeted vectors are random insertion events. Treco, in fact, also teaches that the majority of integration events were not targeted events. In column 21, lines 45–52, Treco indicates that homologous recombination events are masked by a vast excess of events in which integration is by non-homologous recombination.

Treco is relied upon for disclosing methods that will result in non-homologous recombination resulting in the random activation of non-targeted genes such that the Applicants' method is anticipated by Treco. On page 13 of the Office Action, the Examiner states that non-homologous recombination events with the targeted vectors will result in random activation of non-targeted genes "in accordance with the methods of the claimed invention." Applicants submit that neither Treco nor Capecchi, alone or together, can be relied upon to reach this conclusion.

To inherently anticipate, a reference must disclose a claimed limitation to a certainty. Probability or speculation is insufficient. Anticipation by inherency requires that (1) the missing descriptive matter be "necessarily present" in the prior art reference and that (2) it would be so recognized by persons of ordinary skill in the art. *Continental Can Company v. Monsanto,* 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Federal Circuit 1991). For example, if the claimed product was produced in such miniscule amounts and under such conditions that its presence was undetectable, the reference cannot be anticipatory. *In re Seaborg,* 328 F.2d 996, 140 USPQ 662 (CCPA 1964). An accidental or unappreciated duplication of an invention does not defeat the patent right of one who, later in time, was the first to recognize that which constitutes the invented subject matter. *Sylvestri and Johnson v. Grant and Alburn,* 496 F.2d 593 181 USPQ 706, 708 (CCPA 1974).

Furthermore, a retrospective view of inherency cannot substitute for a teaching or suggestion in the art. In deciding that a novel invention would have been obvious there must be supporting teaching in the prior art. Obviousness cannot be predicated on what is unknown. *In re Newell,* 891, F.2d 899 13 USPQ2d 1248, 1250 (Federal Circuit 1989).

In the present case, no evidence of activation was shown by Treco or Capecchi. In fact, Treco teaches that activation can only be achieved by homologous recombination. In column 36, lines 52–53, the reference states that cells in which the transfecting DNA integrates randomly into the genome cannot produce EPO (the target gene). Treco, therefore, actually teaches away from non-homologous recombination to activate endogenous genes.

Accordingly, even if such an activation event accidentally occurred, it would have been unrecognized and unappreciated by the person of ordinary skill in the art as it was unrecognized and unappreciated in the cited reference. Such occurrences do not rise to the level of inherent anticipation. The fact that such events could be achieved was shown for the first time in Applicants' own disclosure.

Moreover, on page 13 of the Office Action the examiner states that "...there are no specific method steps to clearly distinguish between Applicants' process and that normally occurring in any of the targeted homologous recombination schemes described by those in the prior art above." Applicants disagree. Treco retained only homologously recombinant cells, that is, cells expressing the targeted gene. Therefore, only these cells were introduced into an animal. There is no disclosure in Treco of the introduction of non-homologously recombinant cells into an animal. For this reason alone, Treco does not anticipate the invention.

Moreover, there is no motivation to introduce a non-homologously recombinant cell into an animal. Treco teaches away from introducing such a cell by disclosing that the target gene could only be activated by homologous recombination. Treco, therefore, teaches away from making animals from non-homologously recombinant cells.

Accordingly, the cited art neither anticipates nor renders obvious any of the Applicants' claims. Reconsideration and withdrawal of the rejection on these grounds is, therefore, respectfully requested.

In view of the above discussion Applicants submit that the grounds for rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

E. The Rejection Under 35 U.S.C. § 103(a)

On page 14 of the Office Action, claims 81, 83–86, 92 and 100–102 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Sands in view of Schmidt et al., (Molecular and Cellular Biology 10:4406-4411 (1990)). Sands is relied upon as above. Schmidt is relied upon to teach a CMV immediate early promoter. Applicants submit that the reliance on Sands is improper for the reasons given above in response to the rejection under § 102 over Sands.

Schmidt does not compensate for the deficiencies of Sands and is relied upon only for teaching properties of the CMV immediate early promoter. Accordingly, the references, either alone or in combination, do not suggest Applicants' invention. Accordingly, reconsideration and withdrawal of the rejection is requested.

F. The Rejection Under 35 U.S.C. § 103(a)

On page 15 of the Office Action, claims 81, 83, 86, 87, 92 and 100–102 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Sands in view of Bujard et al., U.S. Patent 5,912,411, herein "Bujard." Applicants respectfully traverse the rejection.

Sands is relied upon as discussed above. Bujard is relied upon for teaching an inducible promoter. Sands cannot be relied upon for the reasons discussed above. Bujard does not compensate for the deficiency of Sands in teaching only the utility of transgenic mice carrying a transgene operative linked to an inducible promoter. Accordingly, there is nothing in these references either alone in combination to suggest Applicants' claimed invention. Therefore, reconsideration and withdrawal of the rejection is requested.

G. The Rejection Under 35 U.S.C. § 101

On page 17 of the Office Action, claim 18 has been provisionally rejected under 35 U.S.C. § 101 on the grounds that it claims the same invention as that of claim 58 of co-pending U.S. Application Nos. 09/455,659, 09/513,575, 09/479,123 and 09/513,574, and is claiming the same invention as that of claim 85 co-pending Application No. 09/276,820. Applicants respectfully submit that this rejection is moot in view of the amendment of claim 81 in the present case. However, Applicants do point out that the presence of this claim in each of the above applications is consistent with the restriction requirement issued in the parent case, U.S. Application No. 09/276,820 on September 27, 1999. In any event, since the claim has been amended, reconsideration and withdrawal of the rejection is respectfully requested.

H. The Rejection for Non-Statutory Double-Patenting

On page 17 of the Office Action, claims 83–88, 100, 102 and 103 have been provisionally rejected under the judicially created doctrine of obviousness type double-patenting on the grounds that they are unpatentable over claims 99–104, 128, 131 and 132, respectively of co-pending Application No. 09/276,820.

Applicants submit that upon resolution of the issues in the present case, claims will be appropriately cancelled or amended in one of the two cases, or a terminal disclaimer will be filed.

On page 18 of the Office Action, claims 81, 83–88, 92 and 100–103 are provisionally rejected under the judicially created doctrine of obviousness double-patenting on the grounds that they are unpatentable over claims 81, 83–88, 92 and 100–103, respectively of co-pending Application No. 09/479,122. The Examiner asserts that the claims are not patentably distinct. Applicants respectfully traverse the rejection.

Applicants traverse the rejection because the rejection is inconsistent with the Examiner's restriction requirement in the present case. In the present case, the Examiner restricted the Applicants' invention into 10 groups. Group V was directed to claims 81, 83–88, 92 and 100–103. This group was elected for prosecution in the present case. Claim 81, the only independent claim in Group V, was directed to a method for over-expressing an endogenous

gene in a cell *in vivo* by introducing a vector comprising a transcriptional regulatory sequence into a cell, integrating the vector, over-expressing the gene, screening the cell, and introducing the cell into an animal. Group VI was directed to claims 82–88, 91, 92 and 100–103. Claim 82, the only independent claim in Group VI, was directed to a method for producing an expression production of an endogenous cellular gene *in vivo* by introducing a vector comprising a transcriptional regulatory sequence operably linked to an unpaired splice donor sequence into a cell, integrating the vector into the genome, over-expressing the endogenous gene in the cell, screening the cell for over-expression of the endogenous gene, and introducing the cell into an animal under conditions favoring over-expression of the endogenous gene in the cell *in vivo*. Accordingly, it appears that the Examiner took the position that the method practiced with a vector containing a transcriptional regulatory sequence, was patentably distinct from practicing the method with a vector containing a transcriptional regulatory sequence operably linked to a splice donor sequence.

In U.S. Application No. 09/479,122, claim 81 is directed to a method for over-expressing an endogenous gene in a cell *in vivo* and is practiced with a vector containing a selectable marker, a transcriptional regulatory sequence that is operably linked to an exon comprising a translational start codon, a secretion signal sequence, and an epitope tag sequence, the exon being defined at the 3′ end by an unpaired splice donor site, and wherein the vector does not contain a targeting sequence. The method steps in claim 81, in this case, are the same as the methods steps in claim 81 in the present case. These are as follows: introducing the vector into a cell *in vitro*, integrating the vector into the genome of the cell, over-expressing an

endogenous gene by upregulation of the gene in the cell by the transcriptional regulatory sequence, screening the cell for over-expression of the expression product of the endogenous gene, and over-expressing the endogenous gene in the animal *in vivo*.

If the method practiced with a vector containing a transcriptional regulatory sequence is patentably distinct from practicing the method with a vector containing a transcriptional regulatory sequence operably linked to a splice donor sequence, it is unclear how the method practiced with a vector containing a transcriptional regulatory sequence is not patentably distinct from the method practiced with a vector containing, not only a splice donor, as in the present application, considered patentably distinct by the Examiner in the present application, but also each of the additional elements recited above. Accordingly, Applicants request that the rejection be reconsidered and withdrawn, or that clarification of the apparent inconsistency be provided.

On page 18 of the Office Action, claim 100 is provisionally rejected under the judicially created doctrine of obviousness double-patenting on the grounds that it unpatentable over claim 88 in Application No. 09/481,375, claim 60 of Application Nos. 09/455,659 and 09/513,575, and claim 59 of Application Nos. 09/479, 123 and 09/513,574. Applicants will cancel or amend claims in this or the cited applications, or will provide a terminal disclaimer when substantive issues in the present case are resolved.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants, therefore, respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favorable consideration of this Response is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Amended Claims with Markings to Show Changes Made."**

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 CFR §1.136(a), and any fees required therefore are hereby authorized to be charged to Deposit Account No. **50-0622**, referencing Attorney Docket No. **0221-0003Q.**

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Respectfully submitted,

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AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

83. (Once amended) The method of ~~any one of claims 79, 81 or 82~~ claim 106, wherein said transcriptional regulatory sequence is a promoter.

88. (Once amended) The method of ~~any one of claims 79, 81 or 82~~ claim 106, further comprising introducing double strand breaks into the genomic DNA of said cell prior to or simultaneously with integration of said vector.

92. (Once amended) The method of ~~any one of claims 79, 81 or 82~~ claim 106, wherein said vector ~~construct~~ is linear.

100. (Once amended) The method of ~~any one of claims 76, 79, 81, 82, 93-95, and 97~~ claim 106, wherein said endogenous cellular gene encodes a transmembrane protein.

101. (Once amended) The method of ~~either of claims 81 or 82~~ claim 106, further comprising isolating and cloning said cell prior to introducing said cell into an animal.

102. (Once amended) The method of ~~either of claims 81 or 82~~ claim 106, wherein said animal is a mammal.